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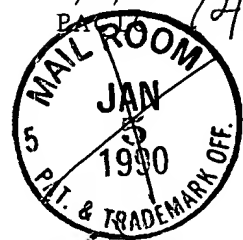
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PATENT APPLICATION
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METHOD FOR TREATING ASTHMA USING
OPTICALLY PURE R(-) ALBUTEROL

Description

Background

05 Albuterol is a drug belonging to the general
class of beta-adrenergic compounds. The prime
action of beta-adrenergic drugs is to stimulate
adenyl cyclase, the enzyme which catalyzes the
formation of cyclic-3',5'-adenosine monophosphate
10 (AMP) from adenosine triphosphate (ATP). The cyclic
AMP formed mediates the cellular responses.
Albuterol acts selectively on beta₂-adrenergic
receptors to relax smooth muscle tissue, for
example, in the bronchial system. Albuterol is most
15 commonly used to treat bronchial spasms associated
with asthma and is the active component in
well-known commercial bronchodilators such as
Proventil and Ventolin.

The form in which albuterol is presently used
20 is a racemic mixture. That is, it is a mixture of
optical isomers, called enantiomers. Enantiomers
are structurally identical compounds which differ
only in that one isomer is a mirror image of the
other and the mirror images cannot be superimposed.
25 This phenomenon is known as chirality. Most biolog-
ical molecules exist as enantiomers and exhibit
chirality. Although structurally identical,
enantiomers can have profoundly different effects in
biological systems: one enantiomer may have a

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specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

05 Summary of the Invention

31 The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(-) albuterol which is
10 active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous
15 system stimulatory effects and cardiac arrhythmia. In these applications, it is important to have a composition which is a potent broncho-dilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition
20 containing the pure R(-) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side
25 effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrhythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and
30 hyperkinesia are reduced when the pure isomer is

administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer
05 reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

Detailed Description of the Invention

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The present invention relies on the broncho-
dilation activity of the R(-) enantiomer of
10 albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present
31 15 method, the optically pure R(-) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from
31 20 bronchial spasms, shortness of breath) is desired. The optically pure R(-) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^1 [(tert-butylamino) methyl]-4-hydroxy-m-
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xylene- α , α' -diol, and to any biologically accept-
25 able salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(-) isomer of
31 albuterol and 10% by weight or less of the S(+) isomer.
30 Optically pure albuterol is readily

obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(-) isomer of albuterol is administered to an individual who has asthma. For example, R(-) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(-) albuterol is administered prophylactically, that is, before the bronchospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(-) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(-) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of

31 administration, for example, by inhaler, nebulizer
or oral administration. About 30 mcg to about 90
mcg of the optically pure R(-) isomer of albuterol
given by inhalation one or more times per day will
05 be adequate in most individuals to produce the
desired bronchodilation effect. For oral
administration, e.g., tablet or syrup, a dose of
about 1 mg to about 8 mg two to four times daily is
administered to produce the desired effect.

31 10 In the method of the present invention, the
optically pure R(-) isomer of albuterol can be
administered together with one or more other
drug(s). For example, an antiasthmatic drug such as
theophylline or terbutaline, or an antihistamine or
15 analgesic such as aspirin, acetaminophen or
ibuprofen, can be given with or in close temporal
proximity to administration of optically pure, R(-)
albuterol. The two (or more) drugs (the optically
pure active isomer of albuterol and another drug)
20 can be administered in one composition or as two
separate entities. For example, they can be
administered in a single capsule, tablet, powder, or
liquid, etc. or as individual compounds. The
components included in a particular composition, in
25 addition to optically pure albuterol and another
drug or drugs, are determined primarily by the
manner in which the composition is to be adminis-
tered. For example, a composition to be
administered in inhalent form can include, in
30 addition to the drug(s), a liquid carrier and/or
propellant. A composition to be administered in

tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

31 In general, according to the method of the present invention, the optically pure R(-) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrhythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(-) isomer may reduce the teratogenic potential associated with albuterol.

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Equivalents

Those skilled in the art will recognize, or be able to ascertain, using no more than routine

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experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.